A kinetic model for amyloid formation in the prion diseases: importance of seeding.

Come JH, Fraser PE, Lansbury PT

Proc Natl Acad Sci U S A 1993 Jul 90:5959-63

BROWSE : Proc Natl Acad Sci U S A • Volume 90 • Issue 13
VIEW : **MEDLINE**, full MEDLINE, related records

Abstract

The transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases characterized by amyloid formation in the brain. The major amyloid protein is the prion protein (PrP). PrP and the beta-amyloid protein of Alzheimer disease share a similar sequence that, in both cases, may be responsible for the initiation of protein aggregation in vivo. We report here that a peptide based on this sequence in PrP (PrP96-111M) forms amyloid fibrils. The existence of a kinetic barrier to amyloid formation by this peptide was demonstrated, suggesting that formation of an ordered nucleus is the rate-determining step for aggregation. Seeding was demonstrated to occur with PrP96-111M amyloid fibrils but not with amyloid fibrils of a related peptide. This effect is consistent with the proposal that the aggregation of PrP, which characterizes TSE, involves a nucleation event analogous to the seeding of a crystallization.

MeSH

Alzheimer Disease; Amino Acid Sequence; Amyloid; Human; Models, Biological; Molecular Sequence Data; Peptide Fragments; Prion Diseases; Prions; Support, Non-U.S. Gov't; Thermodynamics; Virus Replication

Author Address

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 02139.

Order Document

segment (position 701-713) within the highly charged R-domain of CFTR and a region immediately preceding the first transmembrane loop of the sodium channels in both rat brain and eel. The charged R-domain of CFTR is not shared with the topologically closely related P-glycoprotein; the 241 amino acid linking-peptide is apparently the major difference between the two proteins.

In summary, features of the primary structure of the CFTR protein indicate its possession of properties suitable to participation in the regulation and control of ion transport in the epithelial cells of tissues affected in CF. Secure attachment to the membrane in two regions serve to position its three major intracellular domains (nucleotide-binding folds 1 and 2 and the R-domain) near the cytoplasmic surface of the cell membrane where they can modulate ion movement through channels formed either by CFTR transmembrane segments themselves or by other membrane proteins.

In view of the genetic data, the tissue-specificity, and the predicted properties of the CFTR protein, it is reasonable to conclude that CFTR is directly responsible for CF. It, however, remains unclear how CFTR is involved in the regulation of ion conductance across the apical membrane of epithelial cells.

It is possible that CFTR serves as an ion channel itself. As depicted in Figure 13, 10 of the 12 transmembrane regions contain one or more amino acids with charged side chains, a property similar to the brain sodium channel and the GABA receptor chloride channel subunits, where charged residues are present in 4 of the 6, and 3 of the 4, respective membrane-associated domains per subunit or repeat unit. The amphipathic nature of these transmembrane segments is believed to contribute to the channel-forming capacity of these molecules. Alternatively, CFTR may not be an ion channel but instead serve to regulate ion channel activities. In support of the latter assumption, none of the purified polypeptides